

## Aortic valve sclerosis is associated with the extent of coronary artery disease in stable coronary artery disease

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**Background/aim:** Aortic valve sclerosis (AVS) is characterized by lipid deposition and calcific infiltration on the edge of aortic leaflets without significant restriction of motion. The SYNTAX Score (SS) is an important method for evaluating coronary artery disease (CAD). Many studies showed that there is an important relation between the SS and undesired cardiac outcomes. In our study, we investigated the correlation between the SS and AVS by including both ACS and stable CAD cases.

**Materials and methods:** We enrolled 543 patients with CAD who underwent coronary angiography into this cross-sectional study between September 2013 and September 2014.

**Results:** The study population was divided into two groups according to SS values above and below 22. Diabetes mellitus (DM) incidence was greater in the group with high SS values (26.3% vs. 19.2%,  $P = 0.052$ ). Left ventricular ejection fraction (LVEF) and glomerular filtration rate were lower. Low-density lipoprotein cholesterol and triglyceride levels were lower while platelet counts were higher. In multivariate analysis, for the stable coronary artery group AVS existence, platelet count, LVEF value, and chronic obstructive pulmonary disease were found as independent predictors.

**Conclusion:** Our study results demonstrated that AVS is significantly associated with the complexity of CAD, especially in patients with stable CAD. This study provides new information regarding the role of AVS in CAD complexity.

**Key words:** SYNTAX score, aortic valve sclerosis, coronary artery disease

### 1. Introduction

Aortic valve sclerosis (AVS) is defined as increased thickness and progressive calcification of aortic valves that causes no obstruction to ventricular output (antegrade velocity across the valve of less than 2.5 m/s) (1). Histopathological studies demonstrated that causes of AVS are the accumulation of atherogenic lipoproteins, inflammatory cell infiltration, and microscopic calcification in the extracellular matrix (2–4). An independent relation was revealed between atherosclerosis risk factors and clinical cardiovascular disease and AVS. This relation implies that AVS and coronary artery disease (CAD) may have a similar mechanism of formation (5).

The Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score (SS) is an angiographic method for grading the complexity and intensity of CAD and provides more comprehensive

evaluation of properties of the coronary lesion (6–8). Some previous studies showed that a significant correlation between the SS and AVS was revealed in patients with acute coronary syndrome (9). In our study, we investigated the correlation between the SS and AVS by including both ACS and stable CAD cases.

### 2. Materials and methods

We enrolled 543 patients with CAD (stable CAD and acute coronary syndrome without ST segment elevation) who underwent coronary angiography in this cross-sectional study between September 2013 and September 2014. The institutional ethics committee approved the study. Patients with persistent ST segment elevation ( $n = 370$ ), history of percutaneous coronary intervention ( $n = 190$ ) or coronary artery bypass grafting ( $n = 77$ ), rheumatic heart valve disease ( $n = 23$ ), bicuspid aortic valve ( $n = 14$ ), aortic valvular

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velocity above 2 m/s or mild to severe aortic stenosis (n = 14), and SS equal to 0 (n = 103) were excluded from the study.

### 2.1. Data collection and clinical definitions

On admission, baseline clinical characteristics of all patients such as age, sex, body surface area (BSA), body mass index (BMI), hypertension (HT), diabetes mellitus (DM), chronic obstructive pulmonary disease (COPD), chronic renal disease (CRD), glomerular filtration rate (GFR), acute coronary syndrome (ACS), smoking, and previous medications were recorded.

BSA (m<sup>2</sup>) was calculated according to the Mosteller formula ( $\text{height (cm)} \times \text{weight (kg)} / 3600$ )<sup>1/2</sup> and BMI was calculated as  $\text{weight (kg)} / \text{height (m)}^2$ . Hypertension was defined as having at least 2 blood pressure measurements >140/90 mmHg or using antihypertensive drugs. DM was defined as having at least 2 fasting blood sugar measurements >126 mg/dL or using antidiabetic drugs. COPD was defined according to GOLD criteria (FEV1/FVC <0.70). CRD was defined as GFR of <60 mL/min per 1.73 m<sup>2</sup>. GFR was calculated by the Cockcroft–Gault formula ( $(140 - \text{age}) \times (\text{weight (kg)}) / (72 \times \text{creatinine})$ ). ACS was defined according to current guidelines (10,11). During admission to the hospital, blood samples for complete blood count, low-density lipoprotein (LDL)- and high-density lipoprotein (HDL)-cholesterol, triglyceride, and creatinine were obtained from all patients.

### 2.2. SYNTAX score

The SS is used to evaluate the complexity of CAD. Coronary arteries larger than 1.5 mm in diameter and with stenosis of ≥50% were included for evaluation. The online latest updated version (2.11) was used to calculate the SS ([www.SYNTAXscore.com](http://www.SYNTAXscore.com), accessed in October 2014). SSs were divided into 2 groups (low SYNTAX: <22, high SYNTAX: ≥22). All angiographic variables were computed by 2 cardiologists who were unaware of the study data (ST, UA). In the case of disagreement the final decision was made by consensus.

### 2.3. Aortic valve sclerosis

Aortic valves were evaluated from parasternal short axis images. AVS was defined by focal areas of increased echogenicity and thickening of the aortic-valve leaflets without restriction of leaflet motion (aortic velocity <2 m/s).

### 2.4. Statistical analysis

Continuous variables were expressed as mean ± standard deviation or median (interquartile range) and categorical variables were expressed as percentages. The distribution of continuous variables was assessed by Kolmogorov–Smirnov test. Continuous variables between two groups were compared with the Student t-test or Mann–Whitney U test as appropriate. Categorical variables were compared with the chi-square test. To determine independent pre-

dictors of high SSs in the overall population and in the subgroups, multivariate regression analysis was performed. Variables found to be significant (P < 0.05) in univariate analysis were included in multivariate logistic regression analysis. Sensitivity, specificity, negative predictive value (NPV), and positive predictive value (PPV) for AVS in the prediction of high SSs were estimated in 2 × 2 tables. A 2-sided P-value of <0.05 was considered significant. Data were analyzed using SPSS 20.0 (IBM, Armonk, NY, USA).

### 3. Results

Our study includes 543 patients with CAD (median age 62 (52–72) years and 75.7% male). The study population was divided into two groups based on SS values above and below 22. DM incidence was greater in the high SS group (26.3% vs. 19.2%, P = 0.052.). Left ventricular ejection fraction (LVEF) and GFR were lower. LDL-cholesterol and triglyceride levels were lower while platelet counts were higher. Other basal clinical, angiographic, and laboratory characteristics are summarized in Tables 1 and 2.

The overall AVS rate was revealed as 21.2% (n = 115) including all groups. The high SS group had significantly higher AVS positivity compared to the low SS group (31.3% vs. 10.6%, P < 0.001 and OR = 3.8, 95% CI: 2.4–6.1) (Tables 1 and 2; Figure). The LVEF, AVS, GFR, platelet count, TG and LDL levels, and DM existence were significant variables in univariate analysis. Multiple regression analysis were performed with these variables in order to detect the independent predictors of high SS. LVEF, AVS, GFR, platelet count, and LDL levels were evaluated as independent predictors of high SS (Table 3). While there were 28 AVS-positive and 237 AVS-negative cases in the low SS group, there were 87 AVS-positive and 191 AVS-negative cases in the high SS group (Table 4). The sensitivity of AVS positivity to predict high SS was 31%, with a specificity of 89%. PPV and NPV were detected as 75% and 55%, respectively.

In the analysis between AVS and SS parameters, a significant relationship was observed between AVS and bifurcation lesions, ostial lesions, long lesions, and total lesion count (Table 5). In univariate analysis, by dividing patients into two subgroups as the study population with ACS (n = 105) vs. stable CAD (n = 438), DM, LDL and TG levels, AVS existence, platelet count, LVEF value, and COPD existence were found to be significantly related for the stable CAD group, whereas AVS existence, platelet count, LVEF levels, GFR level, and WBC count were found significant for the ACS group. In multivariate analysis, for the stable CAD group, AVS existence, platelet count, LVEF value, and COPD were found as independent predictors, whereas in the ACS group, platelet counts and LVEF values were found as independent predictors (Table 6).

AVS was evaluated with echocardiography by two independent cardiologists unaware of the patient informa-

**Table 1.** Baseline clinical characteristics according to SYNTAX score.

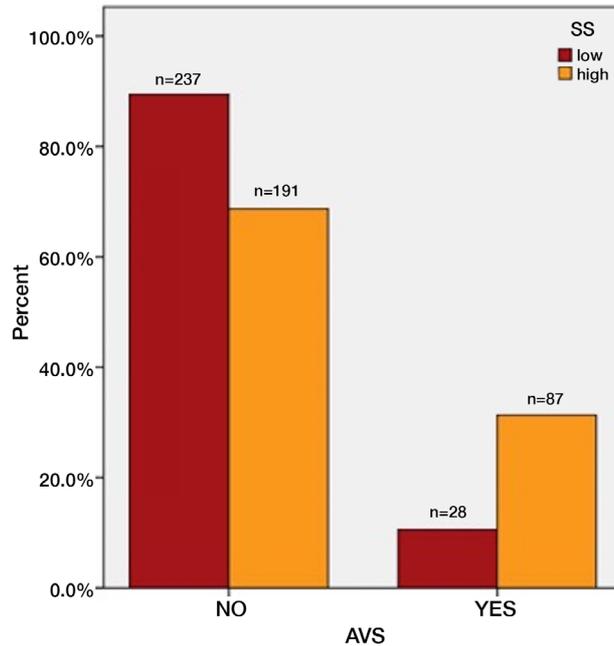
Variables	SYNTAX score <22 (n = 265)	SYNTAX score ≥22 (n = 278)	P-value
Age (years)	62 (49–72)	63 (53–71)	0.474
Male, %	73.2	78.1	0.188
Body surface area, m <sup>2</sup>	1.88 (1.75–2.04)	1.88 (1.72–2.02)	0.625
Body mass index (kg/m <sup>2</sup> )	26 (23–31)	27 (25–30)	0.235
Diabetes mellitus, %	19.2	26.3	0.052
Smoking, %	40.4	37.4	0.478
Hypertension, %	45.7	51.8	0.153
COPD, %	49.1	54.7	0.190
Chronic renal disease, %	15.8	17.6	0.579
Acute coronary syndrome, %	20.0	18.7	0.703
Aortic valve sclerosis, %	10.6	31.3	<0.001
Previous medications, %			
ACE inhibitors	22.6	28.1	0.147
CCB	8.7	9.7	0.677
Beta blocker	6.0	8.3	0.313
Statin	14.7	19.1	0.177
Aspirin	16.6	17.6	0.752
	40.4	37.4	0.478

COPD: Chronic obstructive pulmonary disease, ACE: angiotensin-converting-enzyme, CCB: calcium channel blockers.

**Table 2.** Baseline angiographic and laboratory characteristics according to SYNTAX scores.

Variables	SYNTAX score <22 (n = 265)	SYNTAX score ≥22 (n = 278)	P-value
Vessel, %			
LMCA	16.6	42.8	<0.001
LAD	73.2	85.3	0.001
CX	56.6	53.2	0.431
RCA	62.6	49.3	0.020
Treatment, PCI, %	66	26	<0.001
LV-EF, %	55 (48–62)	47 (39–53)	<0.001
eGFR, mL/min per 1.73 m <sup>2</sup>	92 (68–116)	82 (64–102)	0.030
Creatinine, g/dL	0.88 (0.68–1.17)	0.96 (0.84–1.14)	0.030
Total cholesterol, mg/dL	158 (128–194)	150 (129–190)	0.499
LDL-cholesterol, mg/dL	95 (70–121)	71 (53–99)	<0.001
HDL-cholesterol, mg/dL	38 (32–46)	39 (32–47)	0.608
Triglyceride, mg/dL	121 (84–163)	99 (73–139)	0.002
Hemoglobin, g/dL	14.30 ± 2.43	14.7 ± 1.61	0.160
Platelets, 10 <sup>3</sup> /μL	174 (125–227)	244 (202–294)	<0.001
RDW, %	14 (13.6–14.4)	14 (13.3–14.6)	0.913
WBCs, 10 <sup>3</sup> /μL	8.6 (7.2–11)	8.3 (7.1–10.8)	0.643

LMCA: Left main coronary artery, LAD: left anterior descending, Cx: circumflex, RCA: right coronary artery, PCI: percutaneous coronary intervention, LV-EF: left ventricle ejection fraction, e-GFR: estimated glomerular filtration rate WBCs: white blood cells, RDW: red cell distribution width.



**Figure.** The frequencies of aortic valve sclerosis between low and high SYNTAX scores.

**Table 3.** Multivariate logistic regression analysis to detect the independent predictors of high SYNTAX scores.

Variables	Univariate OR (95% CI)	Univariate P-value	Multivariate OR (95% CI)	Multivariate P-value
LV-ejection fraction	-	<0.001	0.912 (0.880–0.945)	<0.001
Aortic valve sclerosis	3.80 (2.41–6.11)	<0.001	3.312 (1.467–7.480)	0.004
Glomerular filtration rate	-	0.030	0.985 (0.975–0.995)	0.003
Platelets	-	<0.001	1.011 (1.007–1.016)	<0.001
Triglyceride	-	0.002	1.004 (0.996–1.012)	0.300
Diabetes mellitus	1.494 (0.996–2.242)	0.052	1.186 (0.564–2.494)	0.653
LDL-cholesterol	-	<0.001	0.987 (0.975–0.999)	0.039

LV: Left ventricle, LDL: low-density lipoprotein.

**Table 4.** Numbers of aortic valve sclerosis cases between low and high SYNTAX scores.

		SYNTAX score <22	SYNTAX score ≥22	Total
Aortic valve sclerosis	No	237	191	428
	Yes	28	87	115
	Total	265	278	543

tion (İHT, SS). For interobserver agreement, 30 patients were chosen randomly. There was perfect agreement between the two observers (kappa value = 0.842).

**4. Discussion**

In this study, we demonstrated that AVS existence is an important independent predictor to demonstrate the com-

**Table 5.** SYNTAX score parameters according to the presence or absence of aortic valve sclerosis.

SYNTAX variables	AVS (-) (n = 428)	AVS (+) (n = 114)	P-value	OR (95% CI)
Dominance %	84	88	0.306	-
Chronic total occlusion %	27.6	33.8	0.165	-
Bifurcation lesion %	47	64.3	0.010	2 (1.3–3.2)
Ostial lesion %	10	20.2	0.030	2.2 (1.2–3.9)
Diffuse small lesion %	19.4	27	0.690	-
Calcific lesion %	13.8	18.3	0.215	-
Thrombus %	29.7	28.7	0.880	-
Long lesion %	40.9	50.4	0.056	-
Number of total lesions (median)	5 (4–7)	7 (5–8)	<0.001	-

**Table 6.** Multivariate logistic regression analysis to detect the independent predictors of high SYNTAX score in stable coronary artery disease and acute coronary syndrome subgroups.

Variables	Stable coronary artery disease		Acute coronary syndrome	
	Multivariate OR (95% CI)	Multivariate P-value	Multivariate OR (95% CI)	Multivariate P-value
Aortic valve sclerosis	3.114 (1.319–7.351)	0.010	16.2 (0.307–0.855)	0.169
Platelet count	1.012 (1.007–1.016)	<0.001	1.018 (1.004–1.033)	0.014
LV-ejection fraction	0.920 (0.886–0.954)	<0.001	0.829 (0.719–0.955)	0.010
Glomerular filtration rate	-	-	0.974 (0.947–1.010)	0.062
WBCs	-	-	0.742 (0.504–1.093)	0.131
Diabetes mellitus	1.059 (2.364–0.474)	0.890	-	-
LDL-cholesterol	1.005 (0.979–0.992)	0.234	-	-
Triglyceride	1.015 (0.999–1.007)	0.100	-	-
COPD	2.083 (1.064–4.076)	0.032	-	-

LV: Left ventricle, WBCs: white blood cells, LDL: low-density lipoprotein, COPD: chronic obstructive pulmonary disease.

plexity of CAD. We also showed that AVS has significant correlation with SYNTAX parameters like bifurcation lesions, ostial lesions, long lesions, and total lesion count. We showed that the role of AVS to show the complexity of CAD is especially valid for stable CAD, but no significant correlation was seen in the case of ACS with AVS and complexity.

AVS is characterized by lipid deposition and calcific infiltration on the edge of aortic leaflets without significant restriction of motion. AVS incidence has increased with the aging population and common echocardiography use (1,2,4). However, recent studies showed that AVS is not only important because of aging; it may also advance

aortic stenosis and may be related to CAD. Studies have demonstrated that the risk factors for CAD formation and progression may also be the risk factors for AVS development and progression to AD (2,4,5,7,12). We have shown that CAD existence and severity and AVS are related to each other. The mechanisms suggested for the similarity between AVS and atherosclerosis are as follows: 1) AVS has risk factors for atherosclerosis, 2) AVS and atherosclerosis have similar histopathological characteristics, and 3) it was shown that AVS and CAD are related to systemic atherosclerosis, just like the relation of carotid artery disease and peripheral arterial disease with systemic atherosclerosis (2,7,12–15).

The SS is an important method for the evaluation of both the complexity of CAD and determining the treatment protocol (6,8). Many studies showed that there is an important relation between the SS and undesired cardiac outcomes (8,16,17). To date, there are a few studies investigating the relation between the SS and AVS (2,9,15,18). In these studies, ACS cases were included and the relation of the SS with AVS was investigated. We included both AVS and stable CAD, we investigated the relation between AVS and the SS, and we found that AVS is an independent predictor to determine a high SS. In subgroup analysis according to ACS and CAD, we demonstrated that AVS existence predicts a high SS in stable CAD, but not in ACS. However, Korkmaz et al. (9,19) found an important relation between AVS and the SS while including only ACS cases. There are differences between the two studies, like some clinical risk factors and patient numbers. There are also differences for categorical SS values of the two studies. All these factors may describe the discordance of the results of the two studies (9,19). However, we suggest that, despite the SAP group, AVS was not found predictive because those patients in the ACS group were younger and had fewer atherosclerotic risk factors when compared to stable CAD patients. Previously defined and well-known traditional atherosclerotic risk factors such as advanced age, male sex, HT, DM, and smoking are related to stable CAD rather than ACS, and these risk factors have strong correlations

with AVS. In previous studies, it has been demonstrated that AVS and the SS may be related to cardiac mortality and morbidity (2,6,8,9,16,18,19). We also found a strong relation between AVS and the SS and this result supports that AVS is related to the prevalence of CAD and undesired cardiovascular events.

Our study may have clinically important implications. This study initially provides information about the complexity of CAD with AVS in stable CAD cases. However, our study suggests that AVS does not give enough information about the complexity of CAD in ACS cases. For interventional practice, AVS may be related to detection of some complex conditions like chronic total occlusion, bifurcation lesions, and long lesions. Our study has several limitations. Our study was designed as a cross-sectional study, and the number of patients with ACS was relatively low. The absence of an objective echocardiographic method for evaluation of AVS is an important limitation, although there was good inter- and intraobserver agreement. A similar limitation is also present for the SS.

In conclusion, our study results demonstrated that AVS is significantly associated with the complexity of CAD, especially in patients with stable CAD. Moreover, the presence of AVS is correlated with complex lesions such as chronic total occlusion, bifurcation lesions, and long lesions. This study provides new information regarding the role of AVS in CAD complexity.

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